Claims 1, 4-35 are in this application; claims 2 and 3 having been cancelled, claims 1, 4-19, 27, 30 and 33 having been amended, and claims 34-35 added by this amendment.

The rejections under 35 USC 112, ¶2

Claims 30 and 33 were objected to as being indefinite under 35 U.S.C. §112 for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention, with the Examiner referring to the use of the term "freeze-thawing-extrusion" in claim 30, and the comma after consisting of in claim 33.

Claims 30 has been amended to require freeze-thawing followed by extrusion. The amended Claim 30 is supported by the disclosure on pages 26 and 33. Claim 33 has been amended to delete the comma after the phrase consisting of.

Withdrawal of the rejections is respectfully requested in view of the amendment.

The rejection under 35 USC 102(b)

Claims 1-4, 9-11, 16-17, 19 and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Lamparski (Biochemistry, vol. 31., 1992). The Examiner alleges that Lamparski discloses the present invention. More specifically, the Examiner states that Lamparski discloses liposomes containing a phospholipid and a polymerizable colipid and that the polymerizable lipid upon polymerization with UV radiation polymerizes and destabilizes the liposomes thereby leaking the contents.

Claim 1 is now amended to require that the polymerizable colipid at least some of which are in the form of discrete domains within the liposome. This rejection is respectfully traversed in view of the amendment.

Applicants respectively point out that the main phase transition temperature of DOPC is –20°C, DOPE is –10°C and bis-SorbPC used in Lamparski study is 29°C. Therefore, the global transition temperature of the liposomes in Lamparski is substantially below the room temperature and the experimental temperature of 25°C. Consequently, the liposomes prepared and studied in Lamparski were designed to form fluid phase liposomes at room temperature and above. These conditions favor random mixing of the lipids and bis-SorbPC where polymerizable colipids are randomly distributed throughout the liposomal membrane.

Applicants further point out that the main phase transition temperature of PEG-DSPE is 60°C, DSPC is 54.5°C and bis-SorbPC$_{17,17}$ is 29°C. Therefore, in the present invention, the liposomes delivery system comprises a lipid and a polymerizable colipid with main phase transition temperatures above the room temperature. Consequently, there is a phase separation between the two lipids at room temperature and at least some of the lipids exist as discrete domains at room temperature.

Thus the present invention as defined by the amended Claim 1 is distinguishable from the subject matter of Lamparski and the present invention is not anticipated by Lamparski. Withdrawal of the rejection is respectfully requested in view of the amendment.

The rejection under 35 USC 103(a)

Claims 1-5, 9-11, and 16-31 are rejected under 35 U.S.C. §103(a) as being unpatentable over Lamparski. The Examiner alleges it would be obvious to one of ordinary skill in art to use the liposomes of Lamparski for the delivery of the diagnostic

or therapeutic agents with a reasonable expectation of success. The Examiner also states that it would be obvious to one of ordinary skill in art to use any form of ionization as long as they polymerize the lipid.

Claim 1 is now amended to require that the polymerizable colipid at least some of which are in the form of discrete domains within the liposome. This rejection is respectfully traversed in view of the amendment.

Applicants respectively direct the Examiner's attention to Figure 2 and Table 1 of the reference. Lamparski discloses the stability of two-component liposomes composed of polymerizable SorbPC and nonpolymerizable lipid that is either a DOPE or DOPC. Applicants respectfully point to the Examiner that Lamparski only discloses the light-induced destabilization and aqueous contents leakage of liposomes composed of DOPE and SorbPC. The Figure 2 clearly shows that the leakage of liposomal contents results for the liposomes comprising DOPE and SorbPC when there is a loss of monomeric SorPC. However, Figure 2 also clearly demonstrates that photopolymerization of liposomes composed of DOPC and SorbPC does not cause the leakage of the encapsulated contents even after greater than 80% polymerization (note page 689). Therefore, Lamparski teaches that photoinduced polymerization does not destabilize the liposomes composed of DOPC and SorbPC (note Figure 2 and Table 2). Consequently, Lamparski does not teach with a reasonable expectation of success the delivery of diagnostic or therapeutic agents where the polymerizable colipid is irradiated with UV light. On the contrary, Lamparski, if relevant, would appear to teach away from the present invention.

Furthermore, Lamparski does not suggest or teach at all the liposomal delivery system comprising of colipid where at least some of the colipid exist in form of discrete domains within the liposome. As mentioned above, the liposomes prepared and studied in Lamparski has a global transition temperature that is well below the room temperature. Therefore, the polmerizable colipids are randomly distributed throughout the liposomal membrane and no discrete domains exist at room temperature.

By contrast, the claimed liposomal delivery system of the present invention have global transition temperature that is well above the room temperature. Therefore, the nonpolymerizable lipid and the polymerizable colipid exist in solid-like phase and the lipids do not mix with each other. As shown on page 36 of the specification, the liposomal delivery system comprising polymerizable colipid some of which are in form of discrete domains surprisingly enhances the release of the liposomal contents with minimal irradiation.

For example, liposomes prepared from Composition 2 comprising PEG-DSPE, DSPC and bis-SorbPC$_{17,17}$ showed significant release of liposomal contents at much lower ionization radiation doses. Liposomes prepared from Composition 1 comprising PEG-DOPE, DOPC and bis-SorbPC$_{17,17}$ showed significant release of liposome contents at 250 rads compared to only 50 rads for those liposomes prepared from Composition 2. In addition, increasing release for Composition 1 was observed with increasing doses of ionizing radiation up through 2500 rads compared to only 200-250 rads for Composition 2 (note page 36-37 of the specification). These results clearly suggest that a liposome delivery system comprising of a lipid and a polymerizable colipid some of which are in the

form of discrete domains within the liposome enhances the release of the liposomal contents with minimal irradiation.

Applicants respectfully point to the Examiner that the present invention employs ionizing radiation which involves radical species that can initiate radical chain polymerization. Unlike UV radiation, the ionizing radiation is not limited by the depth of penetration or the thickness of the specimen so the liposome-encapsulated or associated diagnostic or therapeutic agents could be released at deeper tissue levels. On the other hand, the UV light can only be used in cases where the target tissue is superficially assessable to the light source. Furthermore, it would place undue reliance on Lamparski teachings since it does not in any way suggest the use of ionizing radiation for the delivery of the diagnostic or therapeutic agents where the polymerizable colipid some of which form discrete domains within the liposome. Withdrawal of the rejection is respectfully requested in view of the amendment.

Claims 5-8 and 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lamparski in view of Woodle (BB 1992). This rejection is respectfully traversed in view of the amendment of claim 1. The Examiner alleges that the inclusion of PEG in liposomes of Lamparski would have been obvious in view of Woodle. However, Woodle only discloses certain sterically stabilized liposomes as pointed out by the Examiner. In addition, Woodle does not suggest the present invention, especially where the liposomes comprise polymerizable colipid. Applicants submit that a person of ordinary skill in the art with Woodle before him would not have been taught or motivated to make liposomal delivery system where at least some of the

polymerizable colipid are in the form of discrete domains within the liposome. Withdrawal of the rejection is respectfully requested in view of the amendment.

Claims 1-33 under 35 U.S.C. §103(a) as being unpatentable over Lamparski by itself or in combination with Woodle in view of Hallahan (US patent no. 6,159,443).

Applicants respectfully disagree.

While Hallahan does mention ionizing radiation and liposomes, the mechanism involved in the liposome delivery system of Hallahan is entirely different from the present invention. Clearly, the Hallahan system does not involve polymerization of a colipid. Hallahan only mentions cross-linking reagents to link functional groups of two difference proteins such as an active agent and a delivery vehicle (note col. 8 line 66 to col. 9 line 54). Therefore, the cross-linking scheme in Hallahan is used only as a way to conjugate the therapeutic agent to the delivery vehicle so the agent can reach the target site. The present invention uses polymerizable colipid some of which are in the form of discrete domains as an efficient way to release the therapeutic agent upon irradiation after it has already reached the target site. Hallahan does not suggest at any time the use of polymerizable colipid as part of the delivery vehicle for therapeutic agents. Applicants submit that a person of ordinary skill in the art with Hallahan before him would not have been taught or motivated to make liposomal delivery system with polymerizable colipid some of which are in the form of discrete domains within the liposome; so that Hallahan does not make claims 1-35 obvious. Withdrawal of the rejection is requested.

Applicants further submit that none of Lamparski, Woodle and Hallahan discloses or in any way suggests that any portion of the polymerizable colipid may be

present in form a discrete domains in the liposomes to achieve an effective liposome delivery system.

New Claims

Claims 34-35 are supported by the disclosure on pages 36 and 37.

Conclusion

Attached hereto is a marked up copy of the changes made to the application by the current amendment. The attached pages are captioned **"Amendments to show changes made".**

Entry of the amendment, and reexamination, reconsideration, and early allowance of claims 1 and 4-35 are respectfully requested.

Respectfully submitted,

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Amendments to show changes made

(Additions in bold, deletions in bold brackets)

1. (Amended) A liposome delivery system, comprising a stable liposome-forming lipid and a polymerizable colipid at least some of which are in the form of discrete domains within the liposome, a fraction of said [which] polymerizable colipid polymerizes upon exposure to ionizing radiation, thereby destabilizing the liposomal membrane.

4. (Amended) The liposome delivery system of claim 1, comprising from about 5 % to about 40 % polymerizable colipid.

5. (Amended) The liposome delivery system of claim 1, wherein the liposome further comprises a steric stabilizer.

6. (Amended) The liposome delivery system of claim 5, comprising from about 2 % to about 20 % steric stabilizer.

7. (Amended) The liposome delivery system of claim 5, comprising from about 5 % to about 40 % polymerizable colipid and from about 2 % to about 20 % steric stabilizer.

8. (Amended) The liposome delivery system of claim 5, wherein the steric stabilizer is a poly (ethylene glycol).

9. (Amended) The liposome delivery system of claim 1, wherein said polymerizable colipid is selected from the group consisting of mono-, bis-, and heterobifunctional, diacetylenyl, acryloyl, methacryloyl, dienoyl, dienyl, sorbyl, muconyl, styryl, vinyl, and lipoyl colipid.

10. (Amended) [A liposomal] The liposome delivery system of claim 1, further comprising a releasable agent.

11. (Amended) The liposome delivery system of claim 10, comprising from about 5 % to about 40 % polymerizable colipid.

12. (Amended) The liposome delivery system of claim 10, wherein the liposome further comprises a steric stabilizer.

13. (Amended) The liposome delivery system of claim 12, comprising from about 2 % to about 20 % steric stabilizer.

14. (Amended) The liposome delivery system of claim 12, comprising from about 5 % to about 40 % polymerizable colipid and from about 2 % to about 20 % steric stabilizer.

15. (Amended) The liposome delivery system of claim 12, wherein the steric stabilizer is a poly (ethylene glycol).

16. (Amended) The liposome delivery system of claim 10, wherein said polymerizable colipid is selected from the group consisting of mono-, bis-, and heterobifunctional, diacetylenyl, acryloyl, methacryloyl, dienoyl, dienyl, sorbyl, muconyl, styryl, vinyl, and lipoyl colipid.

17. (Amended) The liposome delivery system of claim 10, wherein the releasable agent is a water soluble molecule.

18. (Amended) The liposome delivery system of claim 10, wherein the releasable agent is a lipid associated molecule.

19. (Amended) A pharmaceutical composition comprising a liposome delivery system of claim 10, wherein the releasable agent is a therapeutic agent encapsulated in or associated with the liposome, and a pharmaceutically acceptable carrier or diluent.

23. (Amended) A pharmaceutical composition comprising a liposome delivery system of claim 10, wherein the releasable agent is a diagnostic agent encapsulated in or associated with the liposome, and a pharmaceutically acceptable carrier or diluent.

27. (Amended) A method of producing a [radiation sensitive] liposome delivery system of claim 10, comprising the steps of:

(i) drying the lipids that comprise the liposome,

(ii) hydrating said lipids with a buffer, comprising agents to be encapsulated or associated in a desired molar ratio to create hydrated bilayers,

(iii) converting said bilayers into liposomes; and

(iv) purifying the liposomes.

30. (Amended) The method of Claim 27, wherein the bilayers are converted into liposomes by ultrasonification or freeze-thawing[-] followed by extrusion.

33. (Amended) The radiation sensitive liposome of claim 32, wherein the peptide is selected from the group consisting of[,] antibodies, antibody fragments, and antigens.